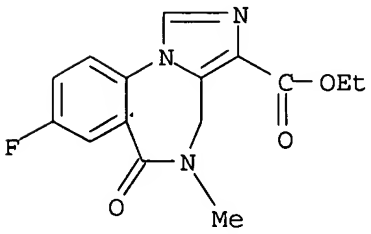
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 78755-81-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN 4H-Imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid,
8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Anexate
CN **Flumazenil**
CN Flumazepil
CN Flumenazil
CN Lanexat
CN Mazicon
CN Ro 15-1788
CN Ro 15-1788/000
CN Ro 151788
CN Ro 1722
CN Ro 41-8157
CN Romazicon
MF C15 H14 F N3 O3
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1539 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1542 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L5 ANSWER 1 OF 2 USPATFULL on STN
AN 2000:109806 USPATFULL
TI 1N-alkyl-N-arylpyrimidinamines and derivatives thereof
IN Aldrich, Paul Edward, Wilmington, DE, United States
Arvanitis, Argyrios Georgios, Kennett Square, PA, United States
Bakthavatchalam, Rajagopal, Wilmington, DE, United States
Beck, James Peter, Smyrna, DE, United States
Cheeseman, Robert Scott, Newtown Square, PA, United States
Chorvat, Robert John, West Chester, PA, United States
Gilligan, Paul Joseph, Wilmington, DE, United States
Hodge, Carl Nicholas, Wilmington, DE, United States
Wasserman, Zelda Rakowitz, Wilmington, DE, United States
PA Dupont Pharmaceuticals Company, Wilmington, DE, United States (U.S. corporation)
PI US 6107301 20000822 <--
AI US 1997-906349 19970805 (8)
RLI Continuation-in-part of Ser. No. US 1994-315660, filed on 29 Sep 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-297274, filed on 26 Aug 1994, now abandoned which is a continuation-in-part of Ser. No. US 1993-134209, filed on 12 Oct 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Ford, John M.
LREP Browder, Monte R., Rubin, Kenneth B.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 8207
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6107301 20000822 <--
AB . . . post-traumatic stress disorders, eating disorders, supranuclear palsy, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and **alcohol** withdrawal symptoms, drug **addiction**, inflammatory disorders, or fertility problems. The novel compounds provided by this invention are those of formula: ##STR1## wherein R.sup.1, R.sup.3,. . .
SUMM . . . stress disorder, supranuclear palsy, eating feeding disorders, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and **alcohol** withdrawal symptoms, drug **addiction**, inflammatory disorders, and fertility problems.
SUMM . . . and in the acoustic startle test (N. R. Swerdlow et al., Psychopharmacology 88:147 (1986)) in rats. The benzodiazepine receptor antagonist (**Ro15-1788**), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner. . .
SUMM . . . neurodegenerative, neuropsychiatric and stress-related disorders such as irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, drug and **alcohol** withdrawal symptoms, drug **addiction**, inflammatory disorders, and fertility problems. It is further asserted that this invention may provide compounds and pharmaceutical compositions suitable for. . .
SUMM . . . post-traumatic stress and eating disorders, supranuclear palsy, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and **alcohol** withdrawal symptoms, drug **addiction**, inflammatory disorders, and fertility problems.
SUMM . . . used for treating affective disorders, anxiety, depression, irritable bowel syndrome, immune suppression, Alzheimer's disease,

gastrointestinal diseases, anorexia nervosa, drug and **alcohol** withdrawal symptoms, drug addition, inflammatory disorders, or fertility problems in mammals.

SUMM . . . method of treating affective disorders, anxiety, depression, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and **alcohol** withdrawal symptoms, drug **addiction**, inflammatory disorders, or fertility problems in mammals in need of such treatment comprising administering to the mammal a therapeutically effective. . .

SUMM . . . amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of **alcohol** and amine functional groups in the compounds of formula (I); and the like.

SUMM . . . water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, **ethanol**, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company,. . .

SUMM . . . can give the 2-chloropurine, LXXV. To prepare the 2-alkoxypurines, LXXVI, LXXV can be heated with a metal salt of the **alcohol** R.sup.31 OH, e.g. the sodium or potassium salt, wherein in R.sup.31 is C.sub.1 -C.sub.4 alkyl. ##STR31##

SUMM The desired formamidine LXXXIII can be treated with LXXXIV in the presence of sodium ethoxide in **ethanol** to give the pyrimidine LXXXV. Refluxing LXXXV in phosphorus oxychloride gives the dichloropyrimidine LXXXVI. Compound LXXXVI can be converted to. . .

SUMM . . . of the amino groups in (CXXIII), (CXXIV), (CXXV), and (CXXVI) via treatment with R.sup.4 I and sodium hydride gave the **desire** (N-pyrimidino-N-alkyl)aminopyrimidines, (CXXVII), (CXXVIII), (CXXIX), and (CXXX). ##STR39##

SUMM . . . with an aliphatic or aromatic amine in an appropriate organic solvent but not limited to, alkyl alcohols such as methanol, **ethanol**, propanol, butanol, alkyl alkanoates such as ethyl acetate, alkanenitriles such as acetonitrile, dialkyl formamides such as DMF gives the corresponding. . .. (CLVI) with appropriate primary amines in an organic solvent such as but not limited to alkyl alcohols such as methanol, **ethanol**, propanol, butanol, alkyl alkanoates such as ethyl acetate, alkanenitriles such as acetonitrile, dialkyl formamides such as DMF, dialkylsulfoxides at temperatures. . .

DETD Part A: A mixture of 2,4-dichloro-6-methylpyrimidine (4 g, 24.54 mmoles), morpholine (2.14 mL, 24.54 mmoles) and N,N-diisopropylethylamine (4.52 mL) in **ethanol** (60 mL) was stirred at 0° C. for 3 hours, 25° C. for 24 hours, followed by reflux for 1. . .

DETD . . . solution of 2-bromo-4-(1-methylethyl)aniline (6 g, 28.2 mmoles) and cyanamide (4.7 g, 112.08 mmoles) dissolved in ethyl acetate (100 mL) and **ethanol** (13 mL) was added hydrogen chloride in ether (1 M, 38 mL, 38 mmoles) and the mixture was stirred at. . .

DETD Part A: A solution of 2,4-dichloro-6-methylpyrimidine (1.0 g) and 2-(methylamino)**ethanol** (0.4 g) in **ethanol** (50 mL) was refluxed for 24 hours. The solvent was evaporated to give a crude residue, which was chromatographed on. . .

DETD Benzyl **alcohol** (197 mg, 1.82 mmol, 1.2 eq) was added slowly to a solution of NaH (73 mg 60% dispersion, 1.82 mmol). . .

DETD . . . mL (118 mmoles) ethyl acetoacetate and 2.0 g (14.47 mmoles) K.sub.2 CO.sub.3 were heated to reflux in 120 mL absolute **ethanol** for 100 hr. Then the solvent was stripped in vacuo and the residue was chromatographed on silica gel using 40%. . .

DETD To 3.05 g (11.69 mmoles) of 4'-amino-3'-iodoacetophenone in a mixture of 40 mL **ethanol** and 10 mL 3 M NaOH was added 2.10 g (25.20 mmoles) methoxyamine hydrochloride and the mixture was heated to reflux for 2 h. The **ethanol** was stripped off in vacuo, the residue was partitioned between 100 mL EtOAc and 30 mL water and the EtOAc.

DETD . . . dried and stripped in vacuo to give 900 mg of the disulfide product, which was dissolved in 10 mL absolute **ethanol** and cooled to 0° C. To that solution 110 mg (2.92 mmoles) of NaBH.sub.4 was added and the mixture was. . .

DETD To 1.05 g (3.33 mmoles) of the ketone of Example 53 in 20 mL absolute **ethanol** cooled to 0° C. was added 127 mg (3.33 mmoles) NaBH.sub.4, and the mixture was allowed to warm to 25°. . . The residue was chromatographed on silica gel using 2:1 EtOAc/hexanes to give 1 g product; mp 46-49° C. The above **alcohol**, 0.72 g (2.27 mmoles), was reacted with 108.09 mg (2.7 mmoles) of NaH (60% in oil) in 5 mL. . .

DETD A solution of 0.2 g (0.58 mmole) 4-N-acetyl-N-methyl-2-methylmercaptoanilinopyrinidine, in 10 mL **ethanol** and 2 mL water containing 272 mg (5 mmoles) KOH was refluxed for 4 h. An additional 200 mg of KOH was added and the heating was continued for 3 h. The **ethanol** was stripped in vacuo and the residue was partitioned between 100 mL EtOAc and 30 mL water. The EtOAc extract. .

DETD Compound XLVII from Scheme 12 above (0.41 g, 0.92 mmol) and sodium borohydride (76 mg. 2 mmol) in 10 mL **ethanol** were stirred for 21 hours at room temperature. The reaction was acidified with 1.0 N hyrdochloric acid, stirred for ten. . .

DETD . . . 29.20 g (0.200 mole) of 2-bromo-4-isopropylaniline in a mixture of 50 mL of glacial acetic acid and 120 mL of **ethanol** was refluxed (nitrogen atmosphere) for two hours. The mixture was stripped of most of the acetic acid and **ethanol** and the residue was taken up in ethyl acetate. This solution was washed with 10% sodium bicarbonate solution, dried with. . .

DETD Part B: To a solution of 10 mL of 1 M potassium tert-butoxide in tetrahydrofuran and a 10 mL of **ethanol** was added 1.11 g (3.65 mmole) of N-(2-bromo-4-isopropyl-phenyl)-aminomethylene-succinonitrile (Part A). The mixture was stirred for 16 hrs under a nitrogen. . .

DETD Part C: A mixture of 18.51 g (0.0609 mole) of 1-(2-bromo-4-isopropylphenyl)-2-amino-4-cyano-pyrrole, 300 mL of **ethanol**, 0.6 mL of conc. hydrochloric acid, and 10 mL (9.75 g, 0.0974 mole) of 2,4-pentanedione was refluxed with stirring under. . .

DETD . . . 1.9 mL (1.94 g; 14.9 mmole) of ethyl acetoacetate, and 0.1 mL of conc. hydrochloric acid in 30 mL of **ethanol** was refluxed for 16 hours. A precipitate formed upon cooling. The precipitate was removed by filtration to give 1.68 g. . .

DETD . . . from Example 64 (part B) and 0.80 mL (0.797 g; 6.03 mmole) of acetoacetaldehyde dimethyl acetal in 20 mL of **ethanol** was added 0.10 mL of conc. hydrochloric acid. The mixture was refluxed for 16 hours, then cooled and evaporated to. . .

DETD Sodium hydride (0.12 g, 3 mmol) and 3-methoxybenzyl **alcohol** (0.41 g, 3 mmol) were reacted in anhydrous THF (10 mL) as for Example 84. A solution of the crude. . .

DETD A mixture of methyl 2-(N-(2-bromo-4-(1-methylethyl)phenyl)-N-ethylamino)-6-methyl-4-pyrimidinaminecarboxylate (Example 18) (10 g, 25 mmol), **ethanol** (100 mL) and a 1N NaOH solution (250 mL) was stirred at reflux temperature for 18 h. After being cooled. . .

DETD Sodium borohydride (0.11 g, 2.8 mmol) was added to a solution of N-(2-bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(3-pyridylcarbonyl)-6-methylpyrimidinamine (0.6 g, 1.4 mmol) in **ethanol** (5 mL). After being stirred for 71 h, the reaction mixture was concentrated in vacuo, treated with a 1N NaOH. . .

DETD Part C: The product of Part B (4.1 g) and Pd/C (10% wt, 0.15 g) were added to **ethanol** (70 mL), methanol (10 mL) and water (1 mL) in a Parr reactor. The reaction mass was treated with hydrogen. . .

DETD To 4,6-dichloro-5-nitropyrimidine (4.16 g, 20 mmol) in **ethanol** (50 mL) was added triethylamine (2.02 g, 20.0 mmol) followed by dropwise addition of bis(2-methoxyethyl)amine (2.7 g, 20.0 mmol) in

ethanol (10.0 mL) over 30 mins at room temperature. After stirring the reaction mixture at room temperature for an additional 1. . .

DETD The product from Part D (255 mg, 0.89 mmol) was suspended in **ethanol** (10 ml), treated with bis(methoxyethyl)amine (656 ml, 4.45 mmol) and brought to reflux for 24 hours. The reaction was concentrated. . .

DETD To the product of Part A of above (3.1 g, 8.45 mmol) was dissolved in **ethanol** (50 mL) and added bis(2-methoxyethyl)amine (1.35 g, 10.1 mmol) followed by triethylamine (1.02 g, 10.1 mmol) and the reaction mixture. . .

DETD The product from example 202 (450 mg, 1.56 mmol) was suspended in **ethanol** (10 ml) and treated with triethylamine (0.261 ml, 1.87 mmol) and bis(2-methoxyethyl)amine (0.277 ml, 1.87 mmol). The reaction was refluxed. . .

DETD . . . amino)-6-methyl-3-nitropyridine. 2,4-Dichloro-6-methyl-3-nitropyridine (4 g, 19.32 mmol) was reacted with dimethoxyethylamine (3.5 mL, 23.66 mmol) in the presence of N,N-diisopropylethylamine in **ethanol** (30 mL) at 25° C. for 60 h and at reflux for 7 h. The product was purified by silica. . .

L5 ANSWER 2 OF 2 USPATFULL on STN
AN 89:56430 USPATFULL
TI Method of medical treatment of **addiction**
IN Tyers, Michael B., Ware, England
PA Glaxo Group Limited, London, England (non-U.S. corporation)
PI US 4847281 19890711 <--
AI US 1987-123369 19871120 (7)
PRAI GB 1986-27909 19861121
DT Utility
FS Granted
EXNAM Primary Examiner: Friedman, Stanley J.
LREP Bacon & Thomas
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 538
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Method of medical treatment of **addiction**
PI US 4847281 19890711 <--
AB . . . of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one and physiologically acceptable salts and solvates thereof in the relief or prevention of a withdrawal syndrome resulting from **addiction** to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse.

SUMM . . . the use of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one and the physiologically acceptable salts and solvates thereof in the treatment of subjects addicted, recovering from **addiction**, or liable to become addicted, to drugs or substances of abuse.

SUMM . . . have now found that the compound of formula (I) may be used in the treatment of subjects addicted, recovering from **addiction**, or liable to become addicted, to drugs or substances of abuse.

SUMM . . . drugs such as opiates (e.g. morphine), cocaine or benzodiazepines (e.g. diazepam, chlordiazepoxide or lorazepam), or substances of abuse such as **alcohol** or nicotine (e.g., smoking) can lead to physical and/or phychological dependence upon that drug or substance. When the drug or. . . of abuse is withdrawn from a dependent subject, the subject develops certain symptoms, such as aggressive behaviour, agitation, and intense **craving** for the drug or substance of abuse. These symptoms may be collectively described as a withdrawal or abstinence sydrome.

SUMM . . . this withdrawal syndrome. The compound is therefore of use for the prevention or relief of a withdrawal syndrome resulting from **addiction** to drugs or substances of abuse.

SUMM . . . formula (I) suppresses dependence on drugs or substances of abuse. The compound is therefore also of use in reducing the **craving** for a drug or substance of abuse after **addiction** to that drug or substance, and can therefore be used for maintainence therapy during remission from addition to drugs or. . .

SUMM The effectiveness of the compound of formula (I) in the treatment of a withdrawal syndome resulting from **addiction** to a drug or substance og abuse, and for the suppression of dependence on a drug or substance of abuse. . . for example, the rat social interaction test, the light/dark exploration test in mice, a marmoset behavioural test and the drinkometer **alcohol** consumption test in rats.

SUMM Accordingly the invention provides a method of treatment for the relief or prevention of a withdrawal syndrome resulting from **addiction** to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse, which. . .

SUMM . . . hydrate) thereof, for use in human or veterinary medicine, for the relief or prevention of a withdrawal syndrome resulting from **addiction** to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse.

SUMM . . . or solvate thereof, for the manufacture of a medicament for the relief or prevention of a withdrawal syndrome resulting from **addiction** to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse.

SUMM . . . cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl **alcohol** or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts,. . .

DETD . . . and dry ether (2+10 ml) and then dried. The resulting solid (0.60 g) was suspended in a mixture of absolute **ethanol** (30 ml) and ethanolic hydrogen chloride (1 ml), and warmed gently to obtain a solution, which was filtered whilst warm. The filtrate was then diluted with dry ether to deposit a solid (0.6 g) which was recrystallised from absolute **ethanol** to give the title compound as a solid (0.27 g) m.p. 186°-187°.

DETD The efficacy of the compound of formula (I) in the treatment of a withdrawal syndrome after **addiction** to a drug or substance of abuse, and for the suppression of dependence on a drug or substance of abuse. . . example in the rat social interaction test, the light/dark exploration test in mice, a marmoset behavioural test and the `drinkometer` **alcohol** consumption test in rats.

DETD Upon abrupt cessation of dosing with diazepam and administration of **RO15-1788**, 10 mg/kg 45 min. before testing, the rats displayed an abstinence syndrome manifest as a reduction in social interaction when. . .

DETD . . . human observer. Such behaviours include vocalisation, posturing, anal scenting, and spending time on the cage front. Following chronic treatment with **alcohol** administered in the drinking water and then abruptly withdrawn, these behaviours are markedly exacerbated.

DETD Thus, in the present experiment marmosets (n=4) were treated with **alcohol** (2% v/v in drinking water) for 30 days. **Alcohol** dosing was abruptly withdrawn, and the marmosets displayed an abstinence syndrome manifest as less time spent on the cage front and an increase in aggressive posturing (A). Administration of the test compound (0.01 mg/kg) twice daily following withdrawal from **alcohol** resulted in a marked attentuation of this abstinence syndrome or abolition when the marmosets were tested on the sixth post-withdrawal. . .

DETD . . . treatment with the test compound, when the animals were given a free choice to consume drinking water which contained either

alcohol or no **alcohol**, the marmosets preferred to abstain from further **alcohol** intake.

DETD

Treatment	(mg/kg)	Aggressive Postures	Time at Cage Front(s)
	Vehicle	9.0	29.4
(A)	**Alcohol** withdrawal	13.8.sup.1	10.6.sup.1
(B)	**Alcohol** withdrawal +	3.0.sup.1 2	77.6.sup.1 2
	Test compound 0.01		

DETD 2p<0.05 vs **alcohol** withdrawal.

DETD The `Drinkometer` **Alcohol** Consumption Test in Rats

DETD Rats given free choice to drink either water containing 2% v/v **alcohol** or water will in time choose to drink **alcohol** solution. The **alcohol** consumed and characteristics of this consumption, such as drinking bouts, indicate that these animals can become dependent upon **alcohol**. In **alcohol** preferring animals, administration of the test compound twice daily in doses of up to 0.01 mg/kg subcutaneously, markedly reduced the amount of **alcohol** consumed over a 24 h period.

CLM What is claimed is:

1. A method of treatment for the relief or prevention of a withdrawal syndrome resulting from **addiction** to a drug or substance or abuse and/or for the suppression of dependence on drugs or substances of abuse, which. . .

8. A method according to claim 1 wherein said drug or substance of abuse is **alcohol**.

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